

## Article

## Synthesis of the Diacetylenic Phospholipids 1,2-(10',12'-Heptadecadiynoyl)-*sn*-Glycero-3-Phosphatidylcholine and 1,2-(4',6'-Tricosadiynoyl)-*sn*-Glycero-3-Phosphatidylcholine

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Fosfatidilcolinas diacetilênicas são compostos análogos aos fosfolípidios naturais. Tais moléculas podem ser hidratadas formando agregados em bicamadas denominados lipossomas, de maneira semelhante às fosfatidilcolinas naturais. Uma característica particular desses lipossomas é a capacidade dos grupos butadiínicos sofrerem polimerização quando submetidos à irradiação com luz ultra-violeta (UV). Este processo possibilita a obtenção de lipossomas polimerizados com propriedades físicas mais apropriadas visando sua aplicação como sistema de liberação controlada de medicamentos. Neste artigo é descrita a síntese total das fosfatidilcolinas diacetilênicas 1,2-bis(10',12'-heptadecadiínoil)-*sn*-glicero-3-fosfatidilcolina (**1a**), 1,2-bis(10',12'-tricosadiínoil)-*sn*-glicero-3-fosfatidilcolina (**1b**) e 1,2-bis(4',6'-tricosadiínoil)-*sn*-glicero-3-fosfatidilcolina (**1c**). Os fosfolípidios **1a** e **1c**, nos quais o cromóforo butadiínil está localizado próximo ao término da cadeia, ou próximo da cabeça polar, respectivamente, não estão relatados na literatura. Também digna de nota é a observação de que liofilização dos intermediários álcoois e ácidos diacetilênicos, reduz significativamente polimerizações indesejadas, permitindo assim o armazenamento desses compostos por algum tempo (~24 h).

Diacetylenic phosphatidylcholines are synthetic compounds analogous to natural phospholipids. These molecules can be hydrated to form bilayered aggregates known as liposomes in a manner similar to natural phosphatidylcholines. A particular feature of these liposomes is their capability of undergoing polymerization when submitted to ultraviolet (UV) light irradiation. This process allows the construction of polymerized liposomes possessing interesting physical properties making these vesicles appropriate for slow-release drug delivering systems. In this article we describe the total syntheses of diacetylenic phosphatidylcholines 1,2-bis(10',12'-heptadecadiynoyl)-*sn*-glycero-3-phosphatidylcholine (**1a**), 1,2-bis(10',12'-tricosadiynoyl)-*sn*-glycero-3-phosphatidylcholine (**1b**) and 1,2-bis(4',6'-tricosadiynoyl)-*sn*-glycero-3-phosphatidylcholine (**1c**). Phospholipids **1a** and **1c**, displaying the butadiinyl chromophores closer to the chain terminus, or closer to the polar heads respectively, have not been reported before. Noteworthy was the observation that liofilization of the diacetylenic alcohols and acids intermediates significantly reduced undesired polymerization, allowing to stock these compounds for a short period of time (~24 h).

**Keywords:** diacetylenic phospholipids, liposomes, polymerizable phospholipid

### Introduction

Diacetylenic groups can be polymerized in the solid-state when exposed to ultra-violet (UV) radiation<sup>1,2,3</sup>. This interesting property has attracted the interest of many researchers for the synthesis of molecules containing diacetylenic moieties for the preparation of special polymers. In 1980 Johnston and coworkers established the first

approach for diacetylenic phosphatidylcholines synthesis<sup>2</sup>. These diacetylenic phospholipids are analogous to the natural products and have potential applications in biology (mimetism of biomembranes) and medicine (polymeric films for improved biocompatibility of implants and stabilized liposomes for drug-delivery)<sup>4,5</sup>.

Phospholipids containing conjugate diyne groups in the acyl chains can undergo polymerization when arranged in monolayers, multilayers or dispersed in aqueous solution (as liposomes) if the temperature is maintained below the gel to

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liquid-crystal transition temperature ( $T_c$ ). This process causes a color change in the system (normally from colorless to orange or red), which allows the detection and indirect quantification of the polymerization by UV/VIS spectroscopy<sup>2,3</sup>. Polymerization depends critically on the packing of monomeric phospholipids in the lipid assemblies. The reaction is topochemical, so the diyne groups must be sufficiently close to each other in the crystalline phase in order to allow polymerization to occur<sup>1,6</sup>. Interestingly, diacetylenic phosphatidylcholines in monomeric liposomes have the capability of forming microtubules after cooling through  $T_c$ <sup>7,8</sup>.

The first syntheses of the diacetylenic phospholipids<sup>2</sup> were based on an asymmetrical Chodkiewicz coupling<sup>9</sup> of an 1-iodoalkyne and an alkynoic acid to generate the required diyne acids. These diyne acids were then coupled to glycerophosphatidylcholine- $\text{CdCl}_2$  complex in the presence of dicyclohexylcarbodiimide (DCC) and DMAP to produce the phospholipids<sup>10</sup>.

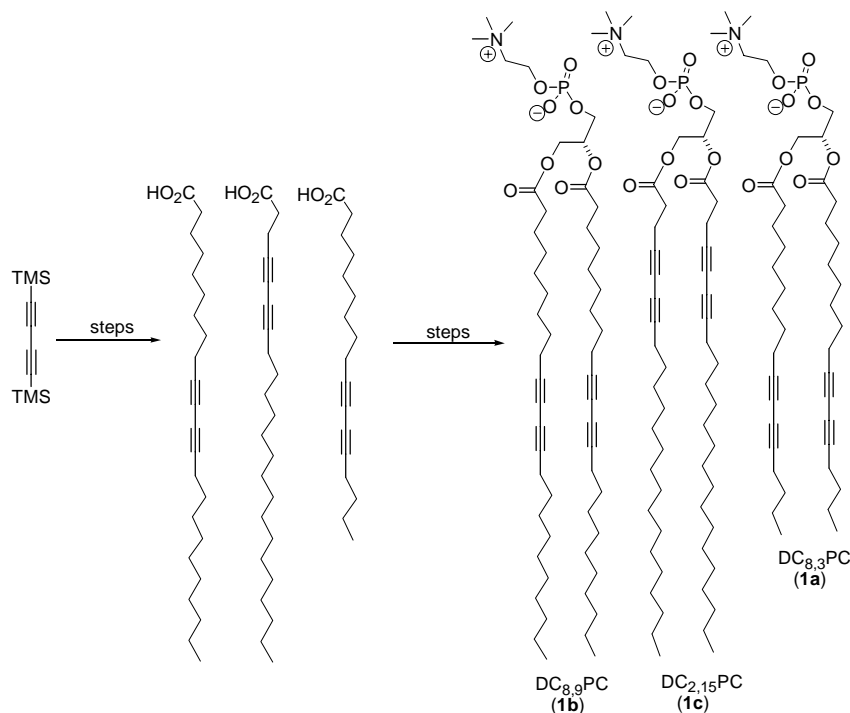
As previously outlined<sup>11</sup>, the main disadvantages of the above method are: (i) the requirement of 1-haloalkynes for the Cadiot-Chodkiewicz reaction; (ii) the low yields for the Cadiot-Chodkiewicz coupling when using higher  $\omega$ -alkynoic acids; and (iii) the frequent contamination of unsymmetrical  $\omega$ -diynoic acids by symmetrical diyne acids. So, a more straightforward method to prepare diacetylenic alcohols and acids was proposed<sup>11</sup>. This alternative route is based on the sequential alkylations of a suitably protected 1,3-butadiyne at its termini with

appropriate alkyl halides. By this procedure, four positional isomers of octadecadiynoic acids and 12,14-pentacosadiynoic and 12,14-heptacosadiynoic acids have been synthesized in good yields.

Due to the good yields reported and the commercial availability of 1,4-bis(trimethylsilyl)-1,3-butadiyne (Aldrich), we decided to use this last synthetic methodology to prepare the 10,12-tricosadiynoic, 4,6-tricosadiynoic and 10,12-heptadecadiynoic acids necessary for the construction of the phospholipids. As described ahead, some modifications/adaptations were necessary to carry out the syntheses in a satisfactory manner. Moreover, two new diacetylenic phosphatidylcholine isomers were synthesized: 1,2-(4',6'-tricosadiynoyl)-*sn*-glycero-3-phosphatidylcholine ( $\text{DC}_{2,15}\text{PC}$  – **1c**) and 1,2-(10',12'-heptadecadiynoyl)-*sn*-glycero-3-phosphatidylcholine ( $\text{DC}_{8,3}\text{PC}$  – **1a**), which differ essentially by the position of diyne groups (C4/C6 and C10/C12). Also, the known phospholipid 1,2-(10',12'-tricosadiynoyl)-*sn*-glycero-3-phosphatidylcholine ( $\text{DC}_{8,9}\text{PC}$  – **1b**), was synthesized. Different positioning of the chromophore should permit further studies to verify the influence of both the diacetylenic group position and the acyl chain length on the polymerization reaction.

## Results and Discussion

The synthesis of the diacetylenic phospholipids was initiated by applying some modifications to the described



**Figure 1.** Diacetylenic fatty acids and diacetylenic phosphatidylcholines prepared in this work.

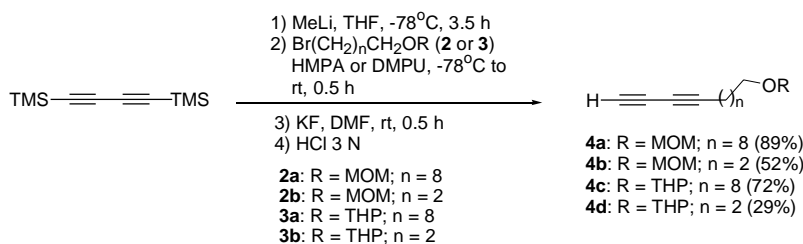
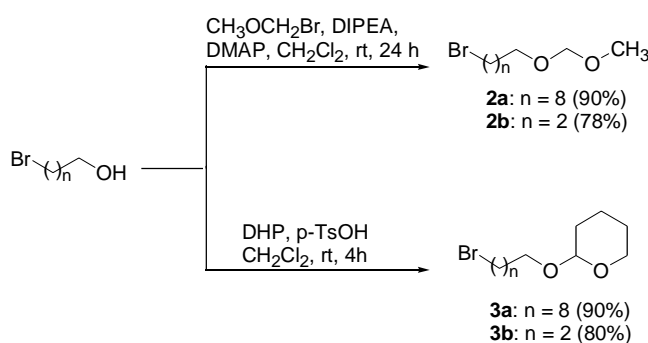
methodology<sup>11</sup> to prepare the MOM-protected  $\omega$ -bromo-1-alkanols **2a-b**. Reaction of 9-bromononanol with methoxymethyl bromide, promoted by DMAP, in presence of DIPEA gave 9-bromo-1-(methoxymethyl)nonane **2a** in excellent yield (90%) and 3-bromo-1-(methoxymethyl)propane **2b** in a good 78% yield. It was observed that protected alkylbromide **2b** was more volatile than alkylbromide **2a**, causing partial loss during purification of this compound (it was obtained in only 68% yield in our first attempted preparation). Other problems with volatility were experienced in the first stages of the synthesis as observed during preparation of compound 7-(methoxymethyl)-1,3-heptadiyne **4b** from **2b** (52% yield). To overcome these difficulties with volatility of compounds **2b** and **4b**, we changed the methoxymethyl (MOM) protecting group for a tetrahydropyran protecting group (THP) having a higher molecular weight. To our satisfaction, protection of 9-bromononanol and 3-bromopropanol with dihydropyran, in presence of catalytic *p*-TsOH provided 9-bromo-1-(tetrahydropyranoxy)nonane **3a** and 3-bromo-1-(tetrahydropyranoxy)propane **3b** in 90% yield and 80% yield respectively (Scheme 1).

Introduction of the 1,3-butadiyne chromophore was done by carrying out monodesilylation of the commercially available 1,4-bis(trimethylsilyl)-1,3-butadiyne with methyllithium, followed by coupling of the intermediate trimethylsilyl-1,3-butadiynyl lithium with the protected alkylbromides **2a-b** or **3a-b**. It is worth mentioning that for an efficient monodesilylation of 1,4-bis(trimethylsilyl)-1,3-

butadiyne strict stoichiometric quantities of methyllithium-lithium bromide complex were required. For this purpose, our batches of methyllithium had its exact concentration evaluated periodically by the Watson-Eastman method<sup>12</sup>. Another critical point for obtaining intermediate **4** was the neutralization step. Therefore, a 0.3N HCl solution was used instead of the 3.0N HCl solution previously described<sup>11</sup>. The terminal diyne **4a** was obtained in 89% yield, while its lower homologue **4b** was prepared in only 52% yield due to its higher volatility. THP-protected compounds **4c** and **4d** were obtained in lower yields (72% and 29%) when compared to the corresponding MOM-protected compounds **4a** and **4b** (Scheme 2). Substitution of HMPA by DMPU was also examined for the preparations of **4c** and **4d**, but yields were unaffected by this modification (Table 1).

**Table 1.** Yields obtained for the preparation of intermediates **4** and **5** when DMPU or HMPA was used.

Compound	Reagent	Yield (%)
<b>4a</b>	HMPA	89
<b>4c</b>	DMPU	72
<b>4c</b>	HMPA	71
<b>4b</b>	HMPA	52
<b>4d</b>	DMPU	26
<b>4d</b>	HMPA	29
<b>5a</b>	HMPA	65
<b>5d</b>	DMPU	73
<b>5b</b>	HMPA	64
<b>5e</b>	DMPU	87
<b>5e</b>	HMPA	58
<b>5c</b>	HMPA	48
<b>5f</b>	DMPU	47



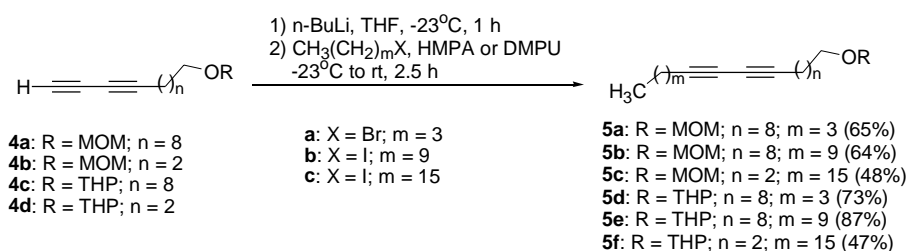
Synthesis of disubstituted diynes went uneventfully. Deprotonation of the terminal diynes with n-BuLi followed by alkylation with the alkylbromides prepared above furnished compounds **5a**, **5b**, **5d** and **5e** in reasonable yields (65%, 64%, 73% and 87%, respectively), and in the same range as those described in the literature<sup>11</sup> for MOM-protected analogous molecules (63% to 79%). Compounds **5c** and **5f** were obtained in slightly lower yields (48% and 47% respectively), therefore MOM and THP protection groups affects reaction yields in a similar way. Moreover, use of DMPU as a replacement for HMPA (a very toxic compound) did not bring any significant change in yields, except for **5e** preparation, as shown in Table 1.

Deprotection of **5a**, **5b**, **5c**, **5d**, **5e** and **5f** was done with HCl 37% in methanol for both MOM-protected and THP-protected compounds, resulting in good yields of the intermediate alcohols **6a-c** (81% to 98%). Alcohols **6b** and **6c** are solids at room temperature and undergo a rather facile polymerization reaction in this aggregation state. Polymerization of **6b** and **6c** can be easily observed as the white color of the solid alcohols turns into a deep blue color within a few minutes. Lyophilization of the alcohols **6b** and **6c** caused a considerable delay in the polymerization reaction, allowing manipulation of them for several hours without detectable color change.

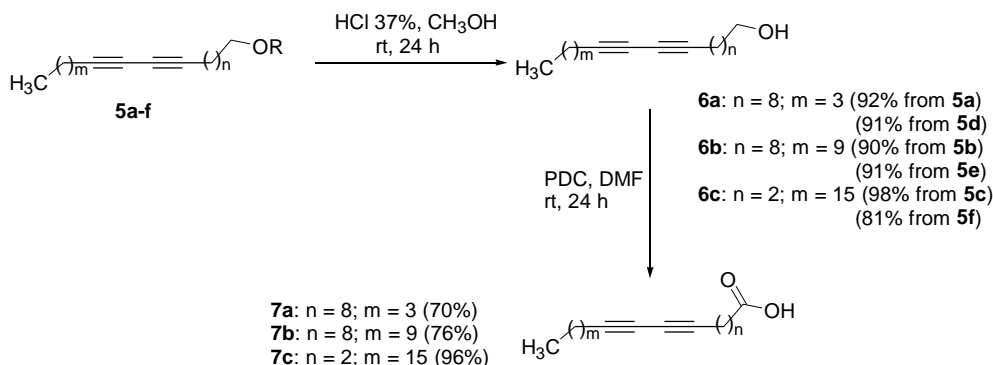
Once optimal conditions for the preparation of alcohols **6a-c** were obtained, they were oxidized to the respective

carboxylic acids. Using PDC as oxidant, diacetylenic acids **7a**, **7b** and **7c** were obtained in good yields (70%, 76% and 96%, respectively). Once again, a premature polymerization had to be avoided at this stage, since the diacetylenic acids undergo rapid polymerization as the solvents are evaporated and the acids become solid. In this case, to avoid polymerization the diacetylenic acids were stored in  $\text{CHCl}_3$  solution at low temperature ( $\sim 4^\circ\text{C}$ ), or in frozen benzene solution (protected from light and under inert atmosphere in both cases). Liofilization from benzene allows manipulation of the diacetylenic acids **7a-c** for a few hours. Scheme 4 shows the conversion of the protected alcohols **5a-f** to the diacetylenic acids **7a-c**. Overall yields of diacetylenic acids **7a** and **7b** synthesized from MOM protected intermediates (**7a**: 37%; **7b**: 39%) were similar to those from THP protected intermediates (**7a**: 33%; **7b**: 43%). In the other hand, overall yield for **7c** synthesis from MOM protected intermediates (23%) was higher than those observed when THP protected intermediates were employed (11%).

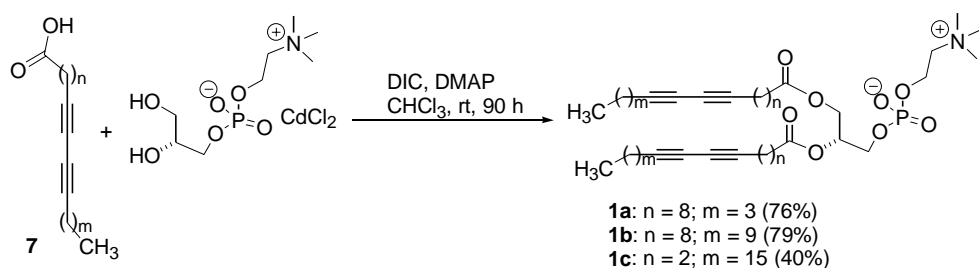
Having obtained the important diacetylenic acid **7a-c** we then turned our attention to the coupling of these carboxylic acids to commercially available L- $\alpha$ -glycerophosphatidylcholine cadmium chloride complex (Sigma). After some experimentation with reactions conditions, the diacetylenic phosphatidylcholines **1a** and **1b** were obtained in good yields (76% and 79%, respectively) employing diisopropylcarbodiimide as the



**Scheme 3.**



**Scheme 4.**



Scheme 5.

coupling agent. Use of DIC as coupling agent led to good yields for the desired phosphatidylcholines **1a** and **1b**. Nevertheless, these same conditions led to the diacetylenic phospholipid **1c** in somewhat lower yields (40%)<sup>13</sup>.

## Experimental

### General Information

Unless noted otherwise, all reactions were carried out under an atmosphere of dry nitrogen or argon, in oven-dried glassware. All solvents were treated in the standard way before use. Flash column chromatography was performed employing Merck silica gel 60 (230-400 mesh). Thin layer chromatography (TLC) was performed on Merck silica gel 60/F-254 aluminum-backed plates, and visualized by UV radiation and/or phosphomolybdic acid and/or potassium permanganate. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (<sup>1</sup>H and <sup>13</sup>C NMR) were recorded as solutions in the indicated solvents on Varian Gemini 300, Bruker AC-300P or Varian INOVA-500 spectrometers. Chemical shifts are reported in parts per million ( $\delta$  units) relative to tetramethylsilane or  $\text{CDCl}_3$  as internal standard (<sup>1</sup>H NMR). When  $\text{CCl}_4$  was used as solvent a capillary containing  $\text{D}_2\text{O}$  was used as internal standard. Infrared spectra were recorded on a Perkin-Elmer 399B, Perkin-Elmer 1600 (FTIR), Nicolet Impact 410 spectrometer or Bomen/MB Series – mod. B100. Low resolution mass spectra were obtained on a Shimadzu QP5000, equipped with a HP-1 column (0.20 x 20m), and high resolution mass spectra on a VG Autospec Instrument. Optical rotations were measured on a Carl Zeiss Polamat A (mercury lamp at 546 nm) and corrected to the sodium D line at 589 nm. Elemental analyses were performed at the Chemistry Institute of the State University of Campinas (Elemental Analyser PE2400).

### General procedure for the preparation of $\omega$ -Bromo-1-(methoxymethyl)alkanols (2):

To a stirred solution of dimethylaminopyridine (DMAP

– 10 mol%) and  $\omega$ -bromo-1-alkanol (3-bromo-1-propanol: 0.707g - 5.1 mmol; 9-bromo-1-nonanol: 2.423g - 10.8 mmol) in dichloromethane (2.0 mL mmol<sup>-1</sup> of  $\omega$ -bromo-1-alkanol) was added dropwise diisopropylethylamine (DIPEA – 300 mol%), and methoxymethyl bromide (300 mol%). The reaction mixture was stirred for 24 h at room temperature. After this period, it was washed with saturated solution of ammonium chloride, sodium bicarbonate 5% solution and saturated sodium chloride solution. The organic layer was dried over sodium sulfate and the solvents removed under vacuum at room temperature. The residue obtained was purified by flash chromatography (eluent: hexane/EtOAc 15:1) and compounds **2a** and **2b** were obtained as colorless liquid.

**9-Bromo-1-(methoxymethyl)nonanol (2a):** ( 2.617g, 90%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  2929, 2854, 1464, 1385, 1244, 1213, 1149, 1111, 1047, 919, 723, 644 (film). <sup>1</sup>H NMR(300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.48 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.42 (t, <sup>3</sup>J 6.4Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.34 (t, <sup>3</sup>J 6.8 Hz, 2H,  $\text{BrCH}_2$ ), 3.26 (s, 3H,  $\text{OCH}_3$ ), 1.27-1.89 (m, 14 H,  $(\text{CH}_2)_7$ ).

**3-Bromo-1-(methoxymethyl)propanol (2b):** ( 0.730g, 78%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  3422, 2930, 2878, 1467, 1441, 1383, 1284, 1258, 1219, 1144, 1111, 1083, 1047, 920, 767, 566. <sup>1</sup>H NMR (300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.52 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.59 (t, <sup>3</sup>J 5.7Hz, 2H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 3.47 (t, <sup>3</sup>J 6.6Hz, 2H,  $\text{BrCH}_2$ ), 3.30 (s, 3H,  $\text{OCH}_3$ ), 2.08 (quintet, <sup>3</sup>J 6.1Hz, 2H,  $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{O}$ ).

### General procedure for the preparation of $\omega$ -bromo-1-(tetrahydropyranyl)alkanols (3):

To a solution of  $\omega$ -bromo-1-alkanol (3-bromo-1-propanol: 1.537g - 11.0 mmol; 9-bromo-1-nonanol: 1.302g - 5.8 mmol) and dihydropyran (250 mol%) in dichloromethane (2.3 mL mmol<sup>-1</sup> of  $\omega$ -bromo-1-alkanol) at room temperature, was added a suspension of *p*-toluenesulfonic acid monohydrate (5 mol%) in dichloromethane. After 6 h (or 19 h when 9-bromo-1-nonanol was employed), the reaction mixture was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic layer was dried over sodium sulfate and the solvents were removed under

vacuum at room temperature. The residue obtained was purified by flash chromatography (eluent: hexane/EtOAc 20:1, or petroleum ether (boiling point 35°C–60°C)/EtOAc 15:1) to afford compounds **3a** and **3b** as colorless liquids.

**9-Bromo-1-(tetrahydropyranyl)nonanol (3a):** (1.617g, 90%). IR  $\nu_{\max}/\text{cm}^{-1}$  2932, 2855, 1453, 1352, 1201, 1135, 1120, 1078, 1033, 905, 869 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.55 (t,  $^3J$  3.6Hz, 1H, OCHO), 3.33–3.87 (m, 6H,  $\text{OCH}_2(\text{CH}_2)_7\text{CH}_2\text{Br}$ ,  $\text{Br}(\text{CH}_2)_9\text{OCHOCH}_2$ ), 1.28–1.86 (m, 20H,  $(\text{CH}_2)_{10}$ ).

**3-Bromo-1-(tetrahydropyranyl)propanol (3b):** (1.960g, 80%). IR  $\nu_{\max}/\text{cm}^{-1}$  3422, 2942, 2869, 1586, 1438, 1349, 1201, 1129, 1077, 1033, 985, 869 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.60 (t,  $^3J$  3.2Hz, 1H, OCHO), 3.83–3.90 (m, 2H,  $\text{OCH}_2(\text{CH}_2)_2\text{Br}$ ), 3.47–3.55 (m, 4H,  $\text{BrCH}_2$ ,  $\text{Br}(\text{CH}_2)_3\text{OCHOCH}_2$ ), 2.13 (quintet,  $^3J$  6.3Hz, 2H,  $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 1.52–1.70 (m, 6H,  $(\text{CH}_2)_3$ ).

*General procedure for the preparation of  $\omega$ -(methoxymethyl)-1,3-alkadiynols and  $\omega$ -(tetrahydro-pyranyl)-1,3-alkadiynols (4):*

To a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (BTMSBD) in THF (2.0 mL mmol $^{-1}$  of BTMSBD) at  $-78^\circ\text{C}$  was added dropwise 1 equivalent of methyl lithium (ether solution). The reaction mixture was maintained under stirring at room temperature for 3.5 h. After this period, a solution of 115 mol% of compound **2** or **3** (**2a**: 0.682g - 2.6 mmol; **2b**: 0.425g - 2.3 mmol; **3a**: 0.787g - 2.6 mmol; **3b**: 0.909g - 4.1 mmols) in HMPA (or DMPU) (2.0 mL mmol $^{-1}$  of BTMSBD) was added dropwise at  $-78^\circ\text{C}$  and the system was maintained under stirring for 30 min at room temperature. Reaction solution was cooled in an ice bath, neutralized with HCl 0.3 mol L $^{-1}$  and extracted with hexane. Solvents of the combined organic layers were removed under vacuum at room temperature, and a slurry of KF (200 mol%) in DMF (2.0 mL mmol $^{-1}$  of BTMSBD) was added to the residue. After stirring during 30 minutes at room temperature, the system was cooled in an ice bath and transferred into a flask containing HCl 3.0 mol L $^{-1}$  (1.5 mL mmol $^{-1}$  of BTMSBD) refrigerated in an ice bath. The layers were isolated and the aqueous one extracted with hexane. Combined organic layers were washed with HCl 3.0 mol L $^{-1}$ , saturated  $\text{NaHCO}_3$ , saturated NaCl, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration, the solvent was removed under vacuum, and the residue obtained was purified by flash chromatography (eluent: hexane/ethyl acetate 15:1; or hexane/ethyl ether 10:1, 7.5:1 and 5:1). Compounds **4a** and **4b** were obtained as light yellow liquids, and compounds **4c** and **4d** were obtained as yellow liquids.

**13-(Methoxymethyl)-1,3-tridecadiyn-13-ol (4a):** (0.473g, 89%). IR  $\nu_{\max}/\text{cm}^{-1}$  3302, 3244, 2931, 2855, 2224, 1465, 1386, 1214, 1145, 1111, 1044, 918, 618 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.48 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.42 (t,  $^3J$  6.5Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.26 (s, 3H,  $\text{OCH}_3$ ), 2.25 (t,  $^3J$  7.0Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 1.82 (s, 1H,  $\text{HC}\equiv\text{C}$ ), 1.32–1.55 (m, 14H,  $(\text{CH}_2)_7$ ).

**7-(Methoxymethyl)-1,3-heptadiyn-7-ol (4b):** (0.160g, 52%). IR  $\nu_{\max}/\text{cm}^{-1}$  3288, 2936, 2884, 2227, 1442, 1383, 1222, 1150, 1112, 1039, 919 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.52 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.55 (t,  $^3J$  5.9Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.29 (s, 3 H,  $\text{OCH}_3$ ), 2.38 (t,  $^3J$  6.9Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 1.97 (s, 1H,  $\text{HC}\equiv\text{C}$ ), 1.75–1.83 (m, 2H,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ).

**13-(Tetrahydropyranyl)-1,3-tridecadiyn-13-ol (4c):** (0.508g, 72%). IR  $\nu_{\max}/\text{cm}^{-1}$  3311, 2932, 2856, 2225, 1466, 1454, 1441, 1352, 1323, 1260, 1201, 1184, 1136, 1120, 1078, 1032, 905, 869, 814 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.57 (t,  $^3J$  3.4Hz, 1H, OCHO), 3.36–3.86 (m, 4H,  $(\text{CH}_2\text{O})_2$ ), 2.24 (t,  $^3J$  7.0Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 1.95 (s, 1H,  $\text{HC}\equiv\text{C}$ ), 1.29–1.89 (m, 8H,  $(\text{CH}_2)_4$ ).

**7-(Tetrahydropyranyl)-1,3-heptadiyn-7-ol (4d):** (0.194g, 29%). IR  $\nu_{\max}/\text{cm}^{-1}$  3301, 2942, 2871, 2361, 2222, 1441, 1353, 1323, 1284, 1258, 1201, 1184, 1134, 1119, 1077, 1033, 985, 932, 869, 815 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.58 (t,  $^3J$  3.3Hz, 1H, OCHO), 3.77–3.86 (m, 2H,  $\text{C}\equiv\text{C}(\text{CH}_2)_2\text{CH}_2\text{O}$ ), 3.42–3.52 (m, 2H,  $\text{C}\equiv\text{C}(\text{CH}_2)_3\text{OCHOCH}_2$ ), 2.39 (t,  $^3J$  7.3Hz, 2H,  $\text{CH}_2\text{C}\equiv\text{C}$ ), 1.96 (s, 1H,  $\text{HC}\equiv\text{C}$ ), 1.51–1.89 (m, 8H,  $(\text{CH}_2)_4$ ).

*General procedure for the preparation of 1-(methoxymethyl)alkadiynols and 1-(tetrahydropyranyl)alkadiynols (5):*

To a solution of **4** (**4a**: 0.387g – 1.6 mmol, for **5a** preparation; **4a**: 0.330g – 1.4 mmol, for **5b** preparation; **4b**: 0.236g – 1.6 mmol; **4c**: 0.707g – 2.56 mmol, for **5d** preparation; **4c**: 1.178g – 4.27 mmol, for **5e** preparation; **4d**: 0.499g – 2.6 mmol) in THF (4 mL mmol $^{-1}$  of **4**) at  $-23^\circ\text{C}$ , was added dropwise 120 mol% of *n*-BuLi (hexane solution). The system was kept under stirring at  $-23^\circ\text{C}$  for 1 h, and then a solution of 120 mol% of 1-haloalkane (**a**, **b** or **c**) in HMPA (or DMPU) (4 mL mmol $^{-1}$  of **4**) was added dropwise. The reaction was maintained at  $-23^\circ\text{C}$  for 30 minutes, and then at rt for 1.5h to 2h. After this period, the solution pH was adjusted to pH 6 with HCl 0.3 mol L $^{-1}$ , and the mixture was extracted with hexane. The combined organic layer was washed with saturated  $\text{NaHCO}_3$ , saturated NaCl, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration, the solvent was removed in vacuum, and the residue obtained was purified by flash chromatography (eluent: hexane/ethyl acetate 20:1) to provide compounds **5a–f** as yellow liquids.

*1-(Methoxymethyl)-10,12-heptadecadiynol (5a)*: (0.311g, 65%). IR  $\nu_{\max}/\text{cm}^{-1}$  3442, 2930, 2856, 1464, 1383, 1322, 1211, 1145, 1112, 1045, 919, 722 (film).  $^1\text{H}$  NMR(300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.48 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.41 (t,  $^3J$  6.4Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.26 (s, 3H,  $\text{OCH}_3$ ), 2.21 (t,  $^3J$  6.0Hz, 4H,  $(\text{CH}_2\text{C}\equiv\text{C})_2$ ), 1.25-1.54 (m, 30H,  $(\text{CH}_2)_{15}$ ), 0.94 (t,  $^3J$  7.1Hz, 3H,  $\omega\text{-CH}_3$ ).

*1-(Methoxymethyl)-10,12-tricosadiynol (5b)*: (0.336g, 64%). IR  $\nu_{\max}/\text{cm}^{-1}$  2927, 2854, 1466, 1385, 1323, 1213, 1146, 1111, 1045, 920, 721 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.61 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.51 (t,  $^3J$  6.6Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.36 (s, 3H,  $\text{OCH}_3$ ), 2.23 (t,  $^3J$  6.9Hz, 4H,  $(\text{CH}_2\text{C}\equiv\text{C})_2$ ), 1.25-1.59 (m, 30H,  $(\text{CH}_2)_{15}$ ), 0.87 (t,  $^3J$  6.6Hz, 3H,  $\omega\text{-CH}_3$ ).  $^1\text{H}$  NMR(300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.47 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.41 (t,  $^3J$  6.4Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.26 (s, 3H,  $\text{OCH}_3$ ), 2.22 (t,  $^3J$  7.0Hz, 4H,  $(\text{CH}_2\text{C}\equiv\text{C})_2$ ), 1.27-1.54 (m, 30H,  $(\text{CH}_2)_{15}$ ), 0.89 (t,  $^3J$  6.8Hz, 3H,  $\omega\text{-CH}_3$ ).

*1-(Methoxymethyl)-4,6-tricosadiynol (5c)*: (0.281g, 48%). IR  $\nu_{\max}/\text{cm}^{-1}$  2926, 2852, 1461, 1373, 1117, 909 (film).  $^1\text{H}$  NMR(300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  4.51 (s, 2H,  $\text{OCH}_2\text{O}$ ), 3.54 (t,  $^3J$  6.0Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.28 (s, 3H,  $\text{OCH}_3$ ), 2.34 (t,  $^3J$  6.9Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2\text{CH}_2(\text{CH}_2)_2\text{O}$ ), 2.22 (t,  $^3J$  6.8Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2(\text{CH}_2)_3\text{O}$ ), 1.77 (quintet,  $^3J$  6.4Hz, 2H,  $(\text{C}\equiv\text{C})_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 1.17-1.52 (m, 28H,  $(\text{CH}_2)_{14}$ ), 0.89 (t,  $^3J$  6.6Hz, 3H,  $\omega\text{-CH}_3$ ).

*1-(Tetrahydropyranyl)-10,12-heptadecadiynol (5d)*: (0.620g, 73%). IR  $\nu_{\max}/\text{cm}^{-1}$  2932, 2857, 1465, 1352, 1322, 1200, 1136, 1121, 1079, 1033, 905, 869, 815 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.57 (t,  $^3J$  3.3Hz, 1H,  $\text{OCHO}$ ), 3.23-3.90 (m, 4H,  $(\text{CH}_2\text{O})_2$ ), 2.20-2.26 (m, 4H,  $(\text{C}\equiv\text{CCH}_2)_2$ ), 1.28-1.83 (m, 24H,  $(\text{CH}_2)_{12}$ ), 0.89 (t,  $^3J$  7.5Hz, 3H,  $\omega\text{-CH}_3$ ).

*1-(Tetrahydropyranyl)-10,12-tricosadiynol (5e)*: (1.550g, 80%). IR  $\nu_{\max}/\text{cm}^{-1}$  2927, 2855, 1466, 1352, 1323, 1200, 1136, 1121, 1079, 1033, 906, 869, 815 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.57 (t,  $^3J$  3.6Hz, 1H,  $\text{OCHO}$ ), 3.33-3.86 (m, 4H,  $(\text{CH}_2\text{O})_2$ ), 2.23 (t,  $^3J$  6.9Hz, 4H,  $(\text{C}\equiv\text{CCH}_2)_2$ ), 1.19-1.74 (m, 36H,  $(\text{CH}_2)_{18}$ ), 0.87 (t,  $^3J$  6.7Hz, 3H,  $\omega\text{-CH}_3$ ).

*1-(Tetrahydropyranyl)-4,6-tricosadiynol (5f)*: (0.513g, 47%). IR  $\nu_{\max}/\text{cm}^{-1}$  2925, 2853, 1466, 1322, 1201, 1158, 1137, 1121, 1076, 1062, 1036, 1020, 991, 869, 816, 721 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  4.58 (t, 1H,  $^3J$  3.4Hz,  $\text{OCHO}$ ), 3.77-3.89 (m, 2H,  $\text{C}\equiv\text{C}(\text{CH}_2)_2\text{CH}_2\text{OCHO}$ ), 3.42-3.54 (m, 2H,  $\text{C}\equiv\text{C}(\text{CH}_2)_3\text{OCHOCH}_2$ ), 2.37 (t,  $^3J$  6.7Hz, 2H,  $\text{C}\equiv\text{CCH}_2(\text{CH}_2)_2\text{O}$ ), 2.30 (t,  $^3J$  6.9Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2(\text{CH}_2)_3\text{O}$ ), 1.18-1.82 (m, 36H,  $\text{C}\equiv\text{CCH}_2\text{-CH}_2\text{-CH}_2\text{O}$ ,  $(\text{CH}_2)_{17}$ ), 0.87 (t,  $^3J$  6.6Hz, 3H,  $\omega\text{-CH}_3$ ).

#### General procedure for the preparation of 1-alkadiynols (6):

To a solution of **5** (**5a**: 0.311g - 1.1 mmol; **5d**: 0.638g - 1.9 mmol; **5b**: 0.229g - 0.6 mmol; **5e**: 0.184g - 0.4 mmol; **5c**: 0.281g - 0.7 mmol; **5f**: 0.491g - 1.2 mmol) in methanol

(25 mL mmol<sup>-1</sup> of **5**) at room temperature was added HCl 37% (3 mL mmol<sup>-1</sup> of **5**). After 24 h, the solvent was evaporated *in vacuum* and water and  $\text{CHCl}_3$  (1:1-v:v) were added to the residue. The system was stirred and aqueous and organic phases were separated. The aqueous layer was extracted with chloroform and the combined organic layer was washed with saturated  $\text{NaHCO}_3$ , saturated NaCl, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was removed under vacuum and the residue obtained was purified by flash chromatography (eluent: hexane/ethanol 6:1; or hexane/ethyl acetate 4:1; or petroleum ether (boiling point 35 °C–60 °C) / EtOAc 5:1, 4:1 and 3:1). Compound **6a** was obtained as a yellow liquid. Alcohols **6b** and **6c** were obtained as white solids after liofilization from benzene solution.

*10,12-Heptadecadiynol (6a)*: (0.432g-0.243g, 91%-92%). IR  $\nu_{\max}/\text{cm}^{-1}$  3345, 2930, 2857, 1465, 1427, 1321, 1056 (film).  $^1\text{H}$  NMR(300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  3.54 (t,  $^3J$  6.2Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.23 (t,  $^3J$  5.7Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2\text{CH}_2(\text{CH}_2)_8\text{OH}$ ), 2.22 (t,  $^3J$  5.8Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2(\text{CH}_2)_9\text{OH}$ ), 1.25-1.54 (m, 19H,  $(\text{CH}_2)_9$ ,  $\text{CH}_2\text{OH}$ ), 0.93 (t,  $^3J$  7.2Hz, 3H,  $\omega\text{-CH}_3$ ).

*10,12-Tricosadiynol (6b)*: (0.182g-0.132g, 90%-91%). IR  $\nu_{\max}/\text{cm}^{-1}$  3413, 2919, 2850, 1468, 1343, 1056, 716 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  3.63 (t,  $^3J$  6.6Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.23 (t,  $^3J$  6.8Hz, 4H,  $(\text{CH}_2\text{-C}\equiv\text{C})_2$ ), 1.19-1.58 (m, 31H,  $(\text{CH}_2)_{15}$ ,  $\text{CH}_2\text{OH}$ ), 0.87 (t,  $^3J$  6.7Hz, 3H,  $\omega\text{-CH}_3$ ).

*4,6-Tricosadiynol (6c)*: (0.318g-0.242g, 81%-98%). mp 56°C-58°C (benzene). IR  $\nu_{\max}/\text{cm}^{-1}$  3202, 2920, 2849, 1471, 1423, 1056, 908, 713 (film).  $^1\text{H}$  NMR(300MHz,  $\text{CCl}_4$ , standard  $\text{SiMe}_4/\text{D}_2\text{O}$ )  $\delta$  3.70 (t,  $^3J$  5.9Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.36 (t,  $^3J$  7.0Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2\text{CH}_2(\text{CH}_2)_2\text{OH}$ ), 2.22 (t,  $^3J$  6.9Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2(\text{CH}_2)_3\text{OH}$ ), 1.73 (quintet,  $^3J$  6.4Hz, 2H,  $(\text{C}\equiv\text{C})_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ ), 1.17-1.52 (m, 29H,  $(\text{CH}_2)_{14}$ ,  $\text{CH}_2\text{OH}$ ), 0.89 (t,  $^3J$  6.9Hz, 3H,  $\omega\text{-CH}_3$ ).

#### General procedure for the preparation of alkadiynoic acids (7):

A solution of PDC (800 mol%) in DMF (8 mL mmol<sup>-1</sup> of **6**) was added to 1-alkadiynol **6** (**6a**: 0.432g - 1.7 mmol; **6b**: 0.157g - 0.5 mmol; **6c**: 0.318g - 1.0 mmol) at room temperature. After 24 h, the reaction was poured into water with stirring. The aqueous layer was extracted with ethyl ether and the combined organic layer was rotaevaporated. The resulting residue was purified by flash chromatography (eluent: hexane/ethanol/85% formic acid 500:100:5; or hexane/ethyl acetate/85% formic acid 500:100:5) to give the alkadiynoic acids **7a-c** as white solids after liofilization from a benzene solution.

*10,12-Heptadecadiynoic acid (7a)*: (0.318g, 70%). IR  $\nu_{\max}/\text{cm}^{-1}$  2923, 2849, 1698, 1465, 1409, 1300, 929 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (t,  $^3J$  7.5Hz, 2H,

$\text{CH}_2\text{COO}$ ), 2.21-2.27 (m, 4H,  $(\text{CH}_2\text{C}\equiv\text{C})_2$ ), 1.25-1.79 (m, 16H,  $(\text{CH}_2)_8$ ), 0.90 (t,  $^3J$  7.1Hz, 3H,  $\omega\text{-CH}_3$ ).  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  180.04 (COOH), 77.42, 77.00, 76.58, 65.27, 65.18, 33.89, 32.48, 30.28, 28.95, 28.92, 28.87, 28.81, 28.76, 28.63, 28.55, 28.17, 26.68, 24.51, 21.80, 19.05, 18.76, 13.39 ( $\omega\text{-CH}_3$ ).

*10,12-Tricosadiynoic acid (7b)*: (0.125g, 76%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  3019, 2924, 2854, 1708, 1464, 1415, 1300, 1216, 932, 758, 726, 669 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (t,  $^3J$  7.5Hz, 2H,  $\text{CH}_2\text{COO}$ ), 2.24 (t,  $^3J$  6.9Hz, 4H,  $(\text{CH}_2\text{C}\equiv\text{C})_2$ ), 1.19-1.65 (m, 28H,  $(\text{CH}_2)_{14}$ ), 0.88 (t,  $^3J$  6.8Hz, 3H,  $\omega\text{-CH}_3$ ).  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  179.59 (COOH), 77.58, 77.40, 76.98, 76.56, 65.27, 65.18, 33.87, 31.84, 29.50, 29.41, 29.25, 29.04, 28.99, 28.92, 28.79, 28.68, 28.29, 28.23, 24.56, 22.61, 19.06, 14.03 ( $\omega\text{-CH}_3$ ).

*4,6-Tricosadiynoic acid (7c)*: (0.320g, 96%). mp 83°C-85°C (benzene), (polymerization). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  2918, 2847, 1689, 1461, 1431, 1214, 1175, 924, 724 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  2.59 (m, 4H,  $\text{C}\equiv\text{C}(\text{CH}_2)_2\text{COO}$ ), 2.24 (t,  $^3J$  7.0Hz, 2H,  $\text{CH}_2(\text{C}\equiv\text{C})_2(\text{CH}_2)_2\text{COO}$ ), 1.18-1.53 (m, 28H,  $(\text{CH}_2)_{14}$ ), 0.88 (t,  $^3J$  6.7Hz, 3H,  $\omega\text{-CH}_3$ ).  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  175.96 (COOH), 78.55, 77.39, 77.16, 76.97, 76.55, 74.41, 66.32, 64.93, 32.58, 31.80, 29.56, 29.34, 29.24, 28.96, 28.76, 28.18, 22.55, 19.06, 14.82, 13.91 ( $\omega\text{-CH}_3$ ).

#### General procedure for the preparation of diacetylenic phosphatidylcholines (1):

To a room temperature suspension of L- $\alpha$ -glycero-phosphatidylcholine cadmium chloride complex (L- $\alpha$ -GPC. $\text{CdCl}_2$  - 100 mol%), 400 mol% of alkadiynoic acid **7** (**7a**: 0.151g - 0.58 mmol; **7b**: 0.156g - 0.45 mmol; **7c**: 0.239g - 0.69 mmol) and DMAP (200 mol%) in anhydrous alcohol free chloroform (16 mL  $\text{mmol}^{-1}$  of L- $\alpha$ -GPC. $\text{CdCl}_2$ ) was added DIC (400 mol%). After 90 h, the reaction mixture was filtered through a short pad of Celite and the solvent evaporated in vacuum. The resulting residue was purified by flash chromatography (eluent: chloroform/methanol/water 65:25:4) to provide the corresponding diacetylenic phospholipids **1a-c** as white solids after liofilization from a benzene solution. When necessary, a second purification by flash chromatography was done using chloroform/methanol/water 80:25:2, 65:25:4 and 50:25:5.

*1,2-(10',12'-Heptadecadiynoyl)-sn-glycero-3-phosphatidylcholine (1a)*: (0.080g, 76%). Elemental analysis (Found: C, 64.37; H, 9.59; N, 1.95 (%)). Calc. for  $\text{C}_{42}\text{H}_{68}\text{NO}_8\text{P}\cdot 2\text{H}_2\text{O}$ : C, 64.49; H, 9.28; N, 1.79 (%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  3392, 2932, 2857, 1737, 1657, 1466, 1426, 1237, 1177, 1089, 1065, 970, 759 (film).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta$  5.17 (m, 1H,  $\text{CH}_2\text{CHCH}_2$ ), 3.80-4.38

(m, 10H,  $\text{POCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{CHCH}_2$ ,  $1\text{H}_2\text{O}$ ), 3.35 (s, 9H,  $\text{N}(\text{CH}_3)_3$ ), 2.21-2.29 (m, 12H,  $(\text{CH}_2\text{COO})_2$ ,  $(\text{CH}_2\text{C}\equiv\text{C})_4$ ), 1.23-1.56 (m, 32H,  $(\text{CH}_2)_{16}$ ), 0.89 (t,  $^3J$  7.3Hz, 6H,  $(\omega\text{-CH}_3)_2$ ).  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  173.57 ( $\text{CH}_2\text{OCO}$ ), 173.22 ( $\text{CH}_2\text{OCO}$ ), 77.38, 76.97, 76.55, 70.56, 70.45, 66.38, 65.26, 63.34, 62.96, 59.30, 54.37, 34.16, 33.96, 30.28, 29.54, 28.99, 28.83, 28.70, 28.56, 28.24, 24.78, 21.77, 19.05, 18.73, 13.33 ( $\omega\text{-CH}_3$ ).

*1,2-(10',12'-Tricosadiynoyl)-sn-glycero-3-phosphatidylcholine (1b)*: (0.084g, 79%). Elemental analysis (Found: C, 65.77; H, 9.91; N, 1.56 (%)). Calc. for  $\text{C}_{54}\text{H}_{92}\text{NO}_8\text{P}\cdot 4\text{H}_2\text{O}$ : C, 65.74; H, 10.22; N, 1.42 (%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  3393, 2919, 2850, 1724, 1651, 1469, 1418, 1238, 1176, 1090, 971, 719 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  5.20 (m, 1H,  $\text{CH}_2\text{CHCH}_2$ ), 3.74-4.47 (m, 16H,  $\text{POCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{CHCH}_2$ ,  $4\text{H}_2\text{O}$ ), 3.31 (s, 9H,  $\text{N}(\text{CH}_3)_3$ ), 2.21-2.29 (m, 12H,  $(\text{CH}_2\text{COO})_2$ ,  $(\text{CH}_2\text{C}\equiv\text{C})_4$ ), 1.25-1.55 (m, 56H,  $(\text{CH}_2)_{28}$ ), 0.87 (t,  $^3J$  6.8Hz, 6H,  $(\omega\text{-CH}_3)_2$ ).  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  173.06 ( $\text{CH}_2\text{OCO}$ ), 172.72 ( $\text{CH}_2\text{OCO}$ ), 77.07, 76.98, 76.90, 76.56, 76.12, 64.87, 64.79, 53.89, 33.79, 33.62, 31.43, 29.10, 29.02, 28.84, 28.74, 28.71, 28.63, 28.53, 28.40, 27.92, 24.43, 24.35, 22.21, 18.73, 13.65 ( $\omega\text{-CH}_3$ ).

*1,2-(4',6'-Tricosadiynoyl)-sn-glycero-3-phosphatidylcholine (1c)*: (0.063g, 40%). Elemental analysis (Found: C, 65.97; H, 10.39; N, 1.54 (%)). Calc. for  $\text{C}_{54}\text{H}_{92}\text{NO}_8\text{P}\cdot 4\text{H}_2\text{O}$ : C, 65.74; H, 10.22; N, 1.42 (%). IR  $\nu_{\text{max}}/\text{cm}^{-1}$  3411, 2918, 2850, 1720, 1656, 1472, 1420, 1233, 1089, 1064, 971, 717 (film).  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta$  5.22 (m, 1H,  $\text{CH}_2\text{CHCH}_2$ ), 3.81-4.42 (m, 12H,  $\text{POCH}_2\text{CH}_2\text{N}$ ,  $\text{CH}_2\text{CHCH}_2$ ,  $2\text{H}_2\text{O}$ ), 3.35 (s, 9H,  $\text{N}(\text{CH}_3)_3$ ), 2.56 (m, 8H,  $(\text{C}\equiv\text{CCH}_2\text{CH}_2\text{COO})_2$ ), 2.23 (t,  $^3J$  7.0Hz, 4H,  $(\text{C}\equiv\text{CCH}_2)_2$ ), 1.20-1.53 (m, 56H,  $(\text{CH}_2)_{28}$ ), 0.87 (t,  $^3J$  6.4Hz, 6H,  $(\omega\text{-CH}_3)_2$ ).  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta$  171.58 ( $\text{CH}_2\text{OCO}$ ), 171.27 ( $\text{CH}_2\text{OCO}$ ), 78.51, 78.43, 77.42, 77.00, 76.58, 74.97, 70.84, 66.13, 66.10, 65.01, 63.46, 63.13, 59.47, 54.38, 32.94, 32.75, 31.84, 29.61, 29.45, 29.27, 29.06, 28.87, 28.28, 22.58, 19.09, 14.91 ( $\omega\text{-CH}_3$ ), 13.98 ( $\omega\text{-CH}_3$ ). MS  $m/z$  (%): 749 ( $\text{M}^+ - 165$ , 5), 403 (6), 327 (10), 313 (16), 286 (11), 169 (31), 145 (18), 131 (28), 91 (38), 71 (53), 57 (100), 55 (84).

## Conclusions

The syntheses of the diacetylenic acids **7a-c** were successfully achieved, which permitted the synthesis of two new DCPC molecules, the 1,2-bis(10',12'-heptadecadiynoyl)-sn-glycero-3-phosphatidylcholine **1a** and the 1,2-bis(4',6'-tricosadiynoyl)-sn-glycero-3-phosphatidylcholine **1c**. The synthetic route to these phospholipids was also made environmental friendly, by replacing HMPA, a highly toxic and mutagenic compound, for DMPU without compromising



practicality and yields. These additive replacements are particularly important for the scale-up of the DCPC synthesis.

Tetrahydropyran (THP) proved to be a reasonable protecting group for the preparation of the 1-bromoalkanol series, since they were less volatile than the MOM protected bromoalkanols **2a,b**.

Also of relevance was the finding that polymerization of the diacetylenic alcohols **6a-c** and of the diacetylenic acids **7a-c** could be suppressed by keeping them in solution. Liofilization of these solutions permitted manipulation of the pure compounds in the solid state without detection of any undesired polymerization reaction for at least a few hours.

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